REMARKS

The Applicants acknowledge the Examiner's acceptance of the amendment dated September 26, 2003, in which claims 32-35 and 37-38 were amended, and claims 9-31 and 36 were cancelled.

The Applicants note with appreciation the withdrawal of the objection to the Specification, in view of the Applicants' amended Specification. The Applicants further note with appreciation the Examiner's withdrawal in part of the rejection of claims 8-9, 31-35, and 37-38 under 35 U.S.C. § 112, first paragraph, and second paragraph.

The Applicants have amended claims 32 and 34 to clarify that the TRAAK potassium channel protein is a "***T***WIK-*r*elated ***a***rachidonic ***a***cid- activated potassium [***K***+] channel" protein. Support for this amendment can be found on page 1 of the Specification. The Applicants have also amended claims 32 and 33 to note that the nucleic acid sequence that is transferred into a cellular host is a functionally equivalent derivative of SEQ ID NOs: 2 and 4, respectively. Support for this amendment can be found on page 6 of the Applicants' Specification. The Applicants have also amended claims 32 and 33 to recite that the functionally equivalent derivatives contain four transmembrane segments and two P domains. Support for this amendment can be found on page 14 of the Specification. It should also be noted that page 6 of the Specification indicates that "functionally equivalent derivatives" refers to derivatives with a sequence comprising a modification and/or suppression and/or addition of one or more amino acid residues, as long as the modification and/or suppression and or addition does not modify the properties of the potassium channel (either TRAAK or TREK-1).

The Applicants have also amended part (d) of claims 32-35 to note that the method measures

the electrophysiological effect of a substance on either a TRAAK of TREK-1 potassium channel protein's current, wherein an increase or decrease in the potassium current indicates modulation of activation of either a TRAAK or TREK-1 potassium channel protein. Support for this amendment can be found on pages 5 and 8 and Figs 8-10. This amendment clarifies that it is the substance, which comes into contact with cellular hosts expressing the TRAAK or TREK-1 potassium channel protein, that modulates the respective TRAAK or TREK's potassium channel current. The modulation of the TRAAK and TREK-1's potassium channel protein's current is exemplified by the results illustrated in Figs 8-10, which show the change in voltage measured in cells expressing TRAAK or TREK-1 when these cells are contacted by a substance capable of modulating the voltage in TRAAK or TREK-1 potassium channel proteins.

The Applicants have also amended claim 33 to clarify that the TREK-1 potassium channel protein is a "TWIK related potassium [K+] channel" protein. Support for this amendment can be found on page 2 of the Specification. The Applicants have also amended claim 33 to note that the nucleic acid sequence that is transferred into a cellular host encodes for a functionally equivalent derivative of SEQ ID NO: 2. Support for this amendment can be found on page 7 of the Applicants' Specification.

The Applicants have also amended claims 34 and 35 to include complements of SEQ ID NO: 2 and 4, respectively. Support for this amendment can be found on page 7 of the Specification. The Applicants have also amended claim 34 and 35 to clarify that the cellular host is cultured under conditions which allow for the expression of the TRAAK and TREK-1 potassium channel proteins. Support for this amendment can be found on page 8 of the Specification. For purposes of clarity, the

Applicants have also amended dependent claims 37-38 to change "process" to "method".

The Applicants have also amended claim 8 to place it into independent form new claim 52, which depends from claim 34. Support for this claim can be found on page 7 of the Specification.

The Applicants have also sequence identifiers to reflect the Applicants Sequence listing submitted September 5, 2000. In particular, the Applicants amended Claim 34 to change "SEQ ID NO: 1" to SEQ ID NO: 2 to reflect that the amino acid sequence associated with TRAAK. The Applicants have also amended Claim 35 to change "SEQ ID NO: 2" to "SEQ ID NO: 4", to reflect that the amino acid sequence associated with TREK-1.

Claims 8, 32-35, and 37-38 are now pending. No new matter has been added as a result of these amendments.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 32-33 and 37-38 have been rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification fails to enable claims 32-33 and claims 37-38 (which depend from claims 32-33). The Applicants submit that as a result of the amendment to claims 32-33, the rejection is now obviated.

In particular, the Applicants have amended claims 32 and 33 so that the claims recite nucleic acid sequences encoding functionally equivalent derivatives of SEQ ID NO: 2 and SEQ ID NO: 4, respectively. These functionally equivalent derivatives must contain four transmembrane segments and two P domains. Further, as recited on page 6 of the Specification, functionally equivalent derivatives are those derivatives which include sequences having a modification and/or suppression and/or addition of one or more amino acid residues as long as the properties of the functionally

equivalent derivative sequence is not modified.

The Applicants submit that the Specification provides sufficient guidance and direction for one skilled in the art to select the Applicants' claimed functionally equivalent derivatives of SEQ ID NOs: 2 and 4. In particular, claims 32 and 33 recite functionally equivalent derivatives of SEQ ID NOs: 2 and 4, which have well-defined structural characteristics that are unique to the claimed potassium channel proteins. These well defined structural features include four transmembrane segments and two P domains. One skilled in the art readily understands that substitutions may be made to a sequence without changing either structural or functional aspects of a polypeptide. Such substitutions generally results when one amino acid of like hydrophobicity, charge, and orientation is substituted with another amino acid having the same or similar properties. One skilled in the art, after studying the Applicants' Specification, would readily be able to determine the proper substitutions so that a functionally equivalent derivative of SEQ ID NOs: 2 and 4, which contain four transmembrane segments and two P domains and can be utilized to screen substances capable of modulating potassium current can be identified.

The reliance on SEQ ID Nos: 2 and 4 as a base sequences, and the detailed structural and functional information recited in claim 32 and 33, allow one skilled in the art to identify candidates of functionally equivalent derivatives of SEQ ID Nos: 2 and 4. These candidate proteins can then be assayed for their electrophysiological properties to determine functional activity according to the protocol set forth on pages 14-19 of the Applicants' Specification. For example, the candidate proteins can be assayed for activation by arachidonic acid and other polyunsaturated fatty acids.

The test for enablement requires an inquiry as to whether one skilled in the art can make or

use the invention without undue experimentation. See MPEP 2164.01. It is well settled in the law that experimentation is **not** undue when the experimentation is routine. Here, it is not undue for the skilled artisan to isolate candidate proteins that meet the structural requirements recited in claims 32 and 33, and assay these candidate protein according to the procedures set forth in pages 14-19 of the Specification. In fact, the Applicants used the procedure set forth in their Specification to isolate and characterize TREK-1 (SEQ ID NO: 4) which is an exemplary functionally equivalent derivative of TRAAK (SEQ ID NO: 2). (See page 6 of the Specification).

The Applicants once again invite the Examiner's attention to the case of *In re Bundy*, wherein the court ruled that appellant's disclosure is sufficient for one skilled in the art to use claimed analogs of a naturally occurring prostaglandin, even though the specification lacked examples of specific analogs, **because the specification had taught that the novel prostaglandin had certain pharmacological properties, which one skilled in the art could test for.** *In re Bundy* 209 USPQ 48, 51-52 (CCPA 1981). [Emphasis added]

Similarly, the Applicants submit that the Applicants' Specification teaches that novel potassium channel proteins have unique pharmacological properties, which can be tested for by using the protocols and guidelines set forth in the Specification. In particular, the unique electrophysiological properties of TRAAK and TREK provide these potassium channel proteins with pharmacological properties that can be readily screened. By way of example, one skilled in the art could follow the protocol set forth in the Applicants' Specification on pages 14-15 and insert a candidate coding sequence based on non-critical variations to either SEQ ID NOs: 2 or 4 in the vector pEXO to synthesize a complementary RNA (cRNA) that can be injected into *Xenopus*

oocytes. (See bottom of page 14 of Specification). Next, a skilled artisan can express the candidate sequence and subclone it into an expression vector under the control of a eukaryotic promoter and then transfect COS cells. (See bottom of page 14 to top of 15 of Specification). A skilled artisan can then determine if the candidate proteins, which were expressed from the candidate nucleotide sequence, contain four transmembrane segments and two P domains. If so, these candidate proteins can then any be subjected to any of a number of the functional assays set forth on pages 14-19 of the Specification to determine the pharmacological properties (i.e. activation by arachidonic acid and polyunsaturated fatty acids and the neuoroprotecitve agent, riluzole). If these substances activate the candidate protein, it is a functional equivalent of SEQ ID Nos. 2 or 4. Consequently, the Applicants submit that the Specification teaches one skilled in the art how to make and use the Applicants' claimed invention without undue experimentation. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection of claims 32 and 33 for lack of enablement.

Claims 32-33 and 37-38 have been rejected under 35 U.S.C. § 112, first paragraph, as lacking written description because allegedly the specification does not demonstrate that the Applicants were in possession of the claimed invention. The Applicants respectfully submit that as a result of the amendment to claims 32-33, the rejection is now obviated.

The current Office Action asserts that "[n]o such proteins or derivatives were made or shown to have activity." The Applicants traverse this assertion, and submit that one of skill in the art would readily understand that the Applicants were in possession of the claimed functionally equivalent derivatives. As can be seen in the Specification, TREK-1 (SEQ ID NO: 4) was an exemplary derivative of the was derived from TRAAK (SEQ ID NO: 2). (See Page 6 of the Specification). This

derivative sequence exhibits the same functional activity pattern as TRAAK (SEQ ID NO: 2). Specifically, arachidonic acid and other polyunsaturated fatty acids, along with the neuroprotective agent riluzole, similarly activate the derivative sequence, TREK-1. Moreover, the Applicants' claim functionally equivalent derivatives of SEQ ID NOs: 2 and 4, which have four transmembrane segments and two P domains, and disclose a quantifiable method of determining whether the functionally equivalent derivatives have TRAAK or TREK-1 activity (e.g., modulation of activation based on the application of certain substances, which include for example, riluzole and arachidonic acid). In light of the Applicants detailed description, representative exemplary functionally equivalent derivative sequence, and disclosure of a method to determine relevant channel activity, one skilled in the art would recognize that the Applicants were in possession of the claimed invention.

The Applicants invite the Examiner's attention to the *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement* ("the guidelines"), which state on page 1106 that:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, **structures**, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety ways including description of... relevant, **identifying characteristics**, structure or other physical and/or chemical properties, **by functional characteristics coupled with a known or disclosed correlation between function and structure**, or by a combination such identifying characteristics, sufficient to show the applicant was in possession of the claimed invention. [Emphasis added].

Here, the Applicants' claims functionally equivalent derivatives of SEQ ID NO: 2 and 4, which are activated by arachidonic acid, other polyunsaturated fatty acids, and riluzole. These functionally

equivalent derivatives have defined structural features, including four transmembrane segments and two P domains. As can be seen in Figs 8 and 9, and in the accompanying description on pages 17-18 of the Specification, these structural features allow TRAAK and TREK to become activated by the aforementioned agents. Thus, the Applicants disclose a structure correlated to a particular function. Consequently, one skilled in the art would readily understand that the Applicants were in possession of functionally equivalent derivatives of SEQ ID Nos: 2 and 4 having four transmembrane segments and 2 P domains, which are correlated to a disclosed function.

Turning to a consideration of the rejection of claims 37 and 38, which alleges that the Specification does not describe the genus of substances that can be used to treat heart disease or central nervous system disorders, the Applicants submit that claimed invention is directed to screening substances, not the substances themselves. The claims are directed to a method of screening substances that are capable of preventing or treating the aforementioned disorders. The Applicants submit that at the time of filing the application, one skilled in the are was aware of a number of substances that could be used to treat heart disease or central nervous system disorders. For example, heart disease related drugs include Pravachol®, Zeztril®, the statins, captopril, lisinopril, fosinopril sodium, and metoprolol. Examples of drugs to treat neurological disorders include Amantadine, Pentobarbital, Gabapentin, and Lithium. New substances are constantly being developed which may treat heart disease or neurological disorders, and the Applicants have developed a method to screen these substances for efficacy in treating/preventing heart disease or neurological disorders. Consequently, the Applicants are not claiming the substances, but rather a method of screening these substances for their efficacy in

treating heart disease and neurological disorders. The claimed screening methods employing novel TRAAK or TREK-1 proteins, or functionally equivalent derivatives thereof which are described and enabled by the Specification. Thus, the claimed screening methods themselves are also described and enabled. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection of claims 32-33 and 37-38 as failing to comply with the written description requirement.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 8, 32-35 and 37-38 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. In accordance with the Examiner's helpful instructions, the Applicants have amended claims 32-35 to relate the method steps back to the preamble. In particular, the Applicants have recited that "an increase or decrease in potassium current indicates modulation of activation of said TRAAK [or TREK-1] protein. Support for this amendment can be found on page 17-18 of the Specification.

In view of the foregoing amendments and remarks, the Applicants submit that the Application is now in condition for allowance, which action is respectfully requested.

Respectfully submitted,

Paul Carango

Paul Carango
Reg. No. 42,386

PC:JEB:pam:vbm
(215) 656-3320